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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,135	12/11/2003	Charles Joel Arntzen	P00245US17	8272

22885 7590 03/19/2009

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ART UNIT	PAPER NUMBER
1638	

MAIL DATE	DELIVERY MODE
03/19/2009	PAPER

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/733,135
Filing Date: December 11, 2003
Appellant(s): ARNTZEN ET AL.

Janae E. Lehman Bell
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed Nov. 17, 2008, appealing from the Office action mailed July 15, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

NEW GROUND(S) OF REJECTION

It is noted that claim 9 includes the additional limitations that are in claim 6 (inclusion of an enhancer and a 5' untranslated leader sequence); therefore, claim 9 should have been rejected with claim 6 under 35 U.S.C. 103(a) as being unpatentable over Goodman et al (US Patent No. 4,956,282, issued on Sept. 11, 1990) in view of Kapikian et al (Reviews of Infectious Diseases (1989) Vol. 11, supplement 3, pp. S539-S546), further in view of Kay et al (Science (1987), Vol. 236, pp. 1299-1302), and further in view of Gallie et al (MGG (1991), Vol. 228, pp. 258-264), rather than with claims 1-5, 7, 8, and 10 in the previous Office Action mailed on July 15, 2008. In this Examiner's Answer claim 9 is included with claim 6 (see below); and this is a new rejection. However, the reasons for the rejection are the same as the reasons set forth previously for claim 6, and the Appellant has stated "Appellant does not rely upon the features of claim 6 for separate patentability apart from the parent claim from which it depends" (see fourth paragraph on page 10 of the Appeal Brief).

The appellant's statement of the grounds of rejection to be reviewed on appeal differs only by the treatment of claim 9, as discussed above.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

4,956,282	Goodman et al	09-1990

EXHIBITS PROVIDED BY EXAMINER IN EXAMINER'S ANSWER

EXHIBIT A: Kapikian et al. Prospects for development of a rotavirus vaccine against rotavirus diarrhea in infants and young children (1989) Reviews of Infectious Diseases; Vol. 11, Supplement 3, pp. S539-S546.

EXHIBIT B: Kay et al. Duplication of CaMV 35S promoter sequences creates a strong enhancer for plant genes. Science (1987), Vol. 236, pp. 1299-1302.

EXHIBIT C: Gallie et al. Post-transcriptional regulation in higher eukaryotes: the role of the reporter gene in controlling expression. MGG (1991), Vol. 228, pp. 258-264.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

A) Claims 1-5, 7, 8, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodman et al (US Patent No. 4,956,282, issued on Sept. 11, 1990) in view of Kapikian et al (Reviews of Infectious Diseases (1989) Vol. 11, supplement 3, pp. S539-S546).

The claims are drawn to a method of producing an immunogenic composition, wherein said method comprises the steps of transforming a plant with a nucleic acid encoding a recombinant viral immunogen, and producing from said plants said composition. Claim 1 includes "selecting those plants expressing said recombinant viral immunogen at a level such that upon oral administration of a composition comprising a plant-expressed recombinant viral immunogen to an animal, an immunogenic response to said viral immunogen is elicited". The office interprets this recitation to be inclusive of selecting plants with any expression level of a viral immunogen because the composition can comprise recombinant viral immunogen that has been purified and/or concentrated; therefore the amount of immunogen in the composition is not related to the level of expression in the plant. Therefore, this part of the claim is not considered a further limitation with regard to any specific or minimal expression level. Claim 4 contains similar language and is therefore inclusive of plants with any expression level. Claims 8 and 9 have no limitation on

the quantity of plant tissue to be administered, and therefore, they are also inclusive of any level of expression.

Goodman et al teach the production of recombinant proteins in plants, including proteins encoded by mammalian viral pathogen genes (see column 3, lines 11-13). They suggest that antigens associated with viral pathogens could be expressed (see column 3, lines 31-32). Antigens are also referred to in the art as immunogens (see page 9 of the instant specification, line 2). They teach that in some instances the recombinant protein can have a physiological effect on ingestion, and it will be sufficient for the product to be retained in an edible plant part (see column 5, lines 51-56). They teach that plants that can be employed for the production of recombinant proteins may be either monocots or dicots (see column 4, lines 55-56), that the DNA construct can be transferred into the plant cell by *A. tumefaciens*, or *A. rhizogenes*, microinjection, liposome fusion, or viral infection (see column 4, lines 43-45) which are all means of transforming a plant with a construct. Goodman et al teach transcriptional initiation regions (also referred to as promoters), including the napin promoter for expression in seeds (which is an edible tissue of a plant) (see column 2, lines 43-58). They suggest the use of several different species of plants that are edible by an animal, including sunflower, corn, sugar cane, soybean, tomato, alfalfa, mustard, and sugar beet (see column 4, lines 59-60). They teach detection of the recombinant protein produced and measurement of the activity of the recombinant protein (see columns 9 and 10).

Goodman et al do not teach an immunogen from a transmissible gastroenteritis virus, nor do they teach an immunogen that is capable of generating an immunogenic response when it interacts with a mucosal membrane.

Kapikian et al teach an immunogen from a transmissible gastroenteritis virus that is capable of generating an immunogenic response when it interacts with a mucosal membrane, (see pages S542-S543 for a discussion of candidate vaccines, and see page S542, right column, last paragraph, where is states that the vaccine was shown to be safe and antigenic after oral administration which shows that is generates an immunogenic response when it interacts with a mucosal membrane). This demonstrates that it has a physiological effect on ingestion.

Given the recognition of those of ordinary skill in the art of the value of expressing an immunogenic protein in a plant as taught by Goodman et al (see column 3, lines 31-42), it would have been obvious to one of ordinary skill in the art to use the method of Goodman et al and to modify said method using the sequences encoding immunogens from the rotovirus taught by Kapikian et al. One would have been motivated to express immunogens from the rotovirus taught by Kapikian et al because they teach that it is important to find a safe, inexpensive, and effective rotavirus vaccine (see page S539, left column, first paragraph) because such a vaccine can prevent diarrheal diseases that cause about 12,600 deaths per day (see page S539, paragraph bridging left and right columns). Furthermore Kipikian et al specifically state that an orally administered vaccine would be the most effective

(see page S541, left column, first paragraph) and Goodman et al specifically suggest that their method can be utilized to grow recombinant viral antigens (see column 3, lines 31-35) and they teach that it could be used for expression in an edible plant part for proteins that can have a physiological effect on ingestion (see column 5, lines 51-56). In addition, it would have been obvious to select the plants with the highest expression levels because common sense dictates that having a higher expression level would be desirable; and the highest producers would have the ability to generate an immunogenic response sufficient to protect against a viral challenge after oral administration of the plant or plant parts. Given the success of producing recombinant therapeutic proteins in plants taught by Goodman et al and the success of utilizing recombinant proteins for vaccines as taught by Kapikian et al, one would expect success in combining the teachings.

Thus, the claimed invention would have been *prime facie* obvious as a whole to one of ordinary skill in the art at the time it was made, especially in the absence of evidence to the contrary.

B) Claims 6 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodman et al (US Patent No. 4,956,282, issued on Sept. 11, 1990) in view of Kapikian et al (Reviews of Infectious Diseases (1989) Vol. 11, supplement 3, pp. S539-S546), as applied to claims 1-5, 7, 8, and 10 above, and further in view of Kay

et al (Science (1987), Vol. 236, pp. 1299-1302), and further in view of Gallie et al (MGG (1991), Vol. 228, pp. 258-264).

The claims are drawn to a method of producing an immunogenic composition, wherein said method comprises the steps of transforming a plant with a nucleic acid encoding a recombinant viral immunogen and comprising a 5' untranslated leader sequence and an enhancer; and producing from said plants said composition.

Goodman et al in view of Kapikian et al have been discussed above. In addition, Goodman et al specifically teach that expression can be directed to a particular plant part such as roots, leaves, stalk, or the like (see column 2, lines 35-37) and they specifically mention the napin promoter or other seed protein promoter for expression in seeds (see column 2, lines 54-58). Depending on the plant; roots, leaves, and seeds can be edible tissues.

Goodman et al in view of Kapikian et al do not teach the use of a 5' untranslated leader sequence, nor do they teach an enhancer sequence.

Kay et al teach the use of an enhancer from the CaMV 35S upstream sequences (see page 1299, middle column).

Gallie et al teach the use of a 5' untranslated leader sequence (see page 258, right column).

Given the recognition of those of ordinary skill in the art of the value of utilizing and enhancer as taught by Kay et al and a 5' untranslated leader sequence as taught by Gallie et al, it would have been obvious to one of ordinary skill in the

art to use the method of Goodman et al and to modify said method by using the enhancer taught by Kay et al and the 5' untranslated leader sequence taught by Gallie et al and by expressing the immunogens taught by Kapikian et al.

One would have been motivated to utilize an enhancer because Kay et al teach that the presence of the enhancer leads to 40-fold higher levels of expression of a transgene (see page 1301, left column, first paragraph).

One would have been motivated to use a leader sequence because Gallie et al teach that a leader sequence substantially enhances translation of a gene construct (see page 258, right column, second paragraph).

One would have been motivated to express the immunogens taught by Kapikian et al because they teach that it is important to find a safe, inexpensive, and effective rotavirus vaccine (see page S539, left column, first paragraph) because such a vaccine can prevent diarrheal diseases that cause about 12,600 deaths per day (see page S539, paragraph bridging left and right columns). Given that Kapikian et al teach that these vaccines can be orally administered and Goodman et al teach that if the particular recombinant protein has a physiological effect upon ingestion then it will not be necessary to purify it out of the edible plant parts, one would have been motivated to express the vaccine in edible plant parts.

Given the successes taught in the prior art, one would expect to succeed in expressing a recombinant viral immunogen utilizing a nucleic acid construct

comprising a leader sequence and an enhancer in the method taught by Goodman et al.

Thus, the claimed invention would have been *prime facie* obvious as a whole to one of ordinary skill in the art at the time it was made, especially in the absence of evidence to the contrary.

(10) Response to Argument

A) The rejections of claims 1-10 under 35 USC 103(a) are proper and should be maintained.

I. The Examiner's conclusion of obviousness is based on the correct application of the law to the claimed invention.

The Appellant argues that the references fail to teach or suggest "selecting those plants expressing said recombinant viral immunogen at a level such that upon oral administration of a composition comprising a plant-expressed recombinant viral immunogen to an animal, an immunogenic response to said viral immunogen is elicited so that the animal is protected against viral challenge" (see page 5 of the Appeal Brief). They argue that the Examiner's interpretation that the claim encompasses any expression level of the immunogen is improper (see first full paragraph on page 6 of the Appeal Brief).

This is not persuasive, however, because this recitation is so broad that it is inclusive of any expression level of the viral immunogen in the plant. This recitation does not specify what animal (human, mouse, rabbit, etc.), it does not specify which viral immunogen (hepatitis B surface antigen, rabies glycoprotein, herpes simplex coat protein, etc.), it does not specify the quantity of immunogen to be administered (10 micrograms, 10 milligrams, 10 grams, a kilogram), it does not specify the quantity of plant material from which the immunogen will be taken (grams or tons) or the quantity of plant material which will be administered for claims 8 and 9, it does not specify the amount of protection against viral challenge (ie. 90% effective, 50% effective, 10% effective) or duration of protection (two weeks, two months, two years, two decades). The Examiner has clearly stated the position of the Office by stating that this recitation is interpreted "to be inclusive of any expression level because the composition can comprise recombinant viral immunogen that has been purified and/or concentrated; therefore the amount of immunogen in the composition is not related to the level of expression in the plant. Therefore, this part of the claim is not considered a further limitation." It is the Examiner's position that if a large enough dose of viral immunogen is given to a subject it will provide at least a small level of protection against viral challenge, and it is the Examiner's position that it is an obvious method step to screen for the plants that express the recombinant protein at the highest levels, therefore the step

of screening for high producers will satisfy this recitation which is so broad as to be inclusive of any expression level.

The Appellant argues that the Examiner has taken a very broad view of Goodman et al and that Goodman et al teach using a transgenic plant to express murine interferon gamma which is adminstered to animals for biological function not for immunogenic properties (see page 6 of the Appeal Brief).

This is not persuasive, however, because Goodman et al clearly suggest production of mammalian viral pathogen genes (see column 3, lines 11-13); and they specifically list antigens associated with viral pathogens, including "the core and envelope proteins of leukemia and lymphotropic retroviruses, such as HTLV-I, -II, and –III, feline leukemia virus, etc., surface antigens of herpes simplex virus, hepatitis B virus, adenovirus, and the like" (see column 3, lines 31-36). It is clear that the teachings of Goodman et al extend beyond their one working example, and it is clear that they have taught and suggested expression of viral antigens. The dictionary definition of antigen is "any substance that can stimulate the production of antibodies"; and this means the same thing as being "immunogenic". The instant specification states that antigens are also referred to in the art as immunogens (see page 9 of the instant specification, line 2). Therefore, the argument that Goodman et al do not teach expression of immunogenic proteins is not a valid argument and is not supported by the facts.

The Appellant asserts that a previous board decision in *Ex parte* Curtiss supports their view of Goodman et al (see paragraph bridging pages 6-7 of the Appeal Brief).

This is not persuasive, however, because the decision was not precedential and the fact patterns were not identical. The excerpt provided includes the statement that "Goodman does not disclose or suggest retaining in the plant a protein which has no effect on ingestion". This is quite different from the rejection that is made in the instant case, because Kapikian et al clearly teach that rotovirus vaccines are effective when administered orally, and therefore the teachings of Kapikian et al provide the element of having a physiological effect on ingestion. For these reasons, the Examiner does not believe that the previous decision is applicable to the instant rejections.

The Appellant argues that the Examiner has failed to properly determine the scope and content of the prior art and ascertain the differences between the prior art and the claims at issue as required under *KSR*.

This is not persuasive, however, because the Examiner has clearly stated that "Goodman et al do not teach an immunogen from a transmissible gastroenteritis virus, nor do they teach an immunogen that is capable of generating an immunogenic response when it interacts with a mucosal membrane". This is the difference between Goodman et al and the instant claims. Clearly Kapikian et al teach these two missing elements, and Kapikian et al provide ample motivation for

why one of ordinary skill in the art would want to, specifically, choose a rotovirus vaccine, because they teach that rotoviruses cause about 12,600 deaths per day (see page S539, paragraph bridging left and right columns).

II. The Examiner has provided a reasonable expectation of success and convincing evidence and line of reasoning for combining Goodman et al with Kapikian et al.

The Appellant argues that Goodman et al contemplate the use of a transgenic plant to produce a protein that is not immunogenic (see third paragraph on page 8 of the Appeal Brief).

This is not persuasive, however, because although Goodman et al reduce to practice a non-immunogenic protein, they clearly teach, suggest, envision, and contemplate expressing viral antigens in plants (see column 3). Antigens are immunogenic, therefore, they clearly contemplate the use of transgenic plants to produce immunogenic proteins. The Appellant's assertion is factually incorrect based upon reading Goodman et al as a whole, and specifically column 3 of Goodman et al.

The Appellant argues that due to viral tropism, a mammalian viral immunogen would normally only be expected to express in a mammalian cell since the virus relies on mammalian host cell factors for expression (see third paragraph on page 8).

This is not persuasive, because Goodman et al clearly teach the production of viral antigen proteins by using plant expression vectors. This does not require infectivity of a host, because the expression is achieved by utilizing a plant promoter, and the plant is stably transformed rather than being infected with the virus. One of ordinary skill in the art would not expect the virus to infect the plant since it is not a plant virus, but one would definitely expect to succeed in producing a viral antigen protein by utilizing plant expression systems.

The Appellant asserts that there is no reasonable expectation of success that a mammalian viral immunogenic protein would be expressed and correctly processed so that it would retain immunogenic properties (see third paragraph on page 8).

This is not persuasive, however, because Goodman et al specifically suggest expressing viral antigens, and they specifically teach that plant systems are good for producing proteins that require folding and/or processing that is unavailable in unicellular microorganisms, and that plants can carry out appropriate processing such as removing transit peptides, glycosylation at glycosylation sites, and folding with appropriate formation of disulfide bonds (see column 3, lines 42-57). Therefore, Goodman et al provide the expectation of success for producing mammalian viral immunogenic proteins in plants.

The Appellant argues that the Examiner failed to identify a reason to combine the references (see paragraph bridging pages 8-9 of the Appeal Brief).

This is not persuasive, however, because the Examiner has clearly set forth reasons to combine. Goodman et al teach that their method would be useful for the production of many different kinds of proteins, including, viral antigens, and they specifically list antigens associated with viral pathogens, including "the core and envelope proteins of leukemia and lymphotropic retroviruses, such as HTLV-I, -II, and –III, feline leukemia virus, etc., surface antigens of herpes simplex virus, hepatitis B virus, adenovirus, and the like" (see column 3, lines 31-36). Their addition of "and the like" at the end of their list is an indication that they do not consider their list to be an exhaustive list of choices. When one takes their suggestion of producing viral antigens in plants, and combines it with the compelling teachings of Kapikian et al about why rotoviruses are especially important, this provides the motivation for specifically producing a viral antigen taken from a rotovirus.

This is ample motivation for one of ordinary skill in the art to combine the teachings. However, even if there were no teaching, suggestion, or motivation to combine, *KSR* forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, - - USPQ2d - - , slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR*, 82 USPQ2d at 1396) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

Furthermore, in *KSR*, the court stated that "the analysis need not seek out precise teaching directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." 127 S.Ct. at 1742, 82 USPQ2d at 1396. The Court in *KSR* noted that "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." 127 S.Ct. at 1742, 82 USPQ2d at 1397.

The Appellant argues that this application claims a benefit of priority to Aug. 26, 1991, and the Appellant cautions against impermissible hindsight (see third paragraph on page 9 of the Appeal Brief).

This is not persuasive, however, because the art relied on was publicly available prior to the priority date of 1991; Goodman et al in 1990 and Kapikian et al in 1989. The Examiner asserts that one of ordinary skill in the art at the time of filing would have been able to make the nexus between the teachings of Goodman et al and Kapikian et al to arrive at a method of making transgenic plants expressing a viral antigen from a rotovirus, and one of ordinary skill in the art would have been motivated to screen for the highest producing plants because of common sense, and one would have expected such a viral antigen to be effective as an orally administered vaccine.

The Appellant states that the additional limitations in claim 6 of an enhancer and a leader sequence are not relied upon for patentability (see fourth paragraph on page 10 of the response). The Examiner notes that this would also apply to claim 9.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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